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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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EXAMINER

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PORTNER, V	
ART UNIT	PAPER NUMBER

1645
DATE MAILED: 10/24/00

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

File Copy

Office Action Summary

Application No.

09/355,793

Applicant(s)

Blaser et al

Examiner

Portner

Group Art Unit

1645



☒ Responsive to communication(s) filed on Aug 3, 2000

☒ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 1, 2, and 4-18 is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 1, 2, and 4-18 is/are rejected.

☒ Claim(s) 15 is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

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DETAILED ACTION

Claims 1-2, 4-18 are pending.

Claims 1,2,4-5 have been amended.

Claim 18 is newly submitted.

Rejections Maintained

1. Claims 10-17 remain rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification for reasons of record in paper number 6.
2. Claims 8, and 14 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for reasons of record in paper number 6.
3. Claims 1-2, 6-8 are rejected under 35 U.S.C. 102(a) as being anticipated by Dworkin et al (March 1996) for reasons of record in paper number 6.
4. Claims 14, and 16 are rejected under 35 U.S.C. 102(b) as being anticipated by Dworkin et al (June 1995) for reasons of record in paper number 6.

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5. Claims 1-2, 4, 6-8 are rejected under 35 U.S.C. 102(b) as being anticipated by Blaser (November 1994 or November 1993) for reasons of record in paper number 6.

6. Claims 1-2,4-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over of Blaser (1994 cited above.) in view of Lubitz et al (US pat. 5,470,573) for reasons of record in paper number 6.

7. Claims 1-2,4-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Blaser (1994 cited above.) in view of Szostak et al (1996).

Incorporation by reference of essential material

8. With respect to applicant's request for clarification, it is the position of the examiner that incorporation of essential material in the specification by reference to a foreign application or patent, or to a publication is improper, the examiner noted that numerous references had been cited at the end of the specification on pages 28 and 29 and were incorporated by reference at page 29, line 21. In response to the enablement rejection made of record in paper number 6, Applicant has pointed to Examples 4 and 9 for enablement of the claimed invention which recite several references, and asserts that they teach essential information and specific aspects to the claimed invention. If these references contain essential information that is only incorporated by reference, then this is improper.

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Please Note: Rejections and objections withdrawn will not be addressed at this time.

Priority

9. The examiner acknowledges the recitation of HIV in the provisional Application.

Response to Arguments

10. The rejection of Claims 10-17 under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification is argued that "Examples 4 and 9 and the reagents required are known to those having ordinary skill in this art as described by Example 4".

11. The RecA protein was known for *Campylobacter jejuni* and the DNA for this gene encoded product could readily be ascertained but the **gene sequence** for the **RecA protein** of **Campylobacter fetus** **was not** in the **public domain** at the time of filing of the priority document dated January 31, 1997. Tummuru et al in 1993 suggested the presence of a putative Chi (RecBCD recognition) site upstream of sapA, sapA1 and sapA2 and suggested a system of homologous recombination, but this does not put the gene in the public domain because the RecA protein and the nucleic acid sequence encoding it were only postulated to be present. A

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suggestion of a gene does not define its existence, nor does it isolate and purify the gene or teach how to make and use the gene. Mutants of the RecA gene of Campylobacter fetus would therefore need to be deposited because the specific gene sequence was not described until after the filing date of the priority document.

12. Applicant's arguments filed with respect to the Deposit requirement for modified bacteria that express SapCDEF genes have been fully considered but they are not persuasive because:

a. The **reference submitted** was **published after the time of filing the instant specification and contains additional information not contained herein.** The submitted reference does not provide for enablement of the claimed invention at the time of filing.

b. Upon consideration of Examples 4 and 9 in the instant specification, the examiner found several references incorporated by reference that provide for guidance for methods and the use of reagents to carry out specific methods steps, but the plasmids recited in Example 4 were not disclosed in the prior art, nor were the gene sequences disclosed. Example 9 refers to strain 23D as the source of the claimed genetic material expressed in modified bacteria. The strain from which the genes were isolated

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was not defined as a publicly available strain of C.fetus and therefore does not meet the requirements under the Budapest Treaty. The only strain disclosed for attainment of the SapCDEF genes is strain 23D. No other strains were used in the attainment of these genes. In view of the prior art, as well as the instant specification, teaching that natural recombination within this bacterium is a well established fact, the use of the disclosed restriction enzymes in an attempt to pull out the genes contained in the claimed modified strain of bacteria would not be predictable nor repeatable.

c. While strain 23D was described, the strain did not meet the Deposit requirement under the Budapest Treaty. Deposit of the strain that comprises the SapCDEF genes so they could be obtained by the method of the instant specification would meet the enablement requirement for the claimed invention.

d. Deposit of the plasmids that encode the genes for SapC, SapD, SapE and SapF would also define a means for providing a repeatable method for obtaining strains of bacteria that would express these genes. This requirement was not made of record previously and is not being made now but is being defined as an alternative means for meeting the enablement of the claimed modified bacteria that express SapCDEF genes.

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e. The instant specification does not teach that any strain of C.fetus may be used for the attainment for the recited genes using the disclosed restriction endonuclease patterns. Only a single strain of C.fetus has been described, strain 23D, which has a specific endonuclease pattern shown in the drawings. Only this pattern has been provided in order to obtain the genes to enable how to make and use the claimed invention. One of skill in the art could use this strain given the guidance provided to obtain the claimed genes to produce a modified (transformed host cell) bacteria. The genetic material contained in the claimed genes is defined by the strain from which it was obtained in view of the high degree of genetic recombination that this locus undergoes.

f. The Deposit requirement is maintained.

13. Applicant argues the rejection of Claim 8, under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention by asserting that claim 1 does not recite the word antigen.

14. Applicant's arguments filed with respect to claim 8 above, have been fully considered but they are not persuasive because claim 1 does recite the word "antigen", see line 3 of original claim 1, last word. Claim 8 broadens the scope of claim 1 that recites only the use of a heterologous antigen. Claim 8 recites the word antigen again, and adds an additional limitation of therapeutic

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agents. The rejection of claim 8 under 35 U.S.C. 112, second paragraph is maintained for reasons of record.

15. Applicant argues the rejection of Claim 14, under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention by asserting that the sequence of the gene was published in the Journal of Bacteriology, 1998.

16. Applicant's arguments filed with respect to claim 14 above, have been fully considered but they are not persuasive because the reference was **published after the effective filing date** of the claimed invention. The instantly claimed invention is a 371 of PCT/US98/01780 filed January 30, 1998. The gene sequence was not described in the PCT Application from which this Application finds its priority date. The instant application defines plasmids that encode the recited genes and a strain of bacteria 23D that has been shown to evidence specific palindromes that are cut by the endonucleases used in the instant specification but no specific gene sequences are defined in the instant specification. Therefore, the rejection under 35 U.S.C. 112, second paragraph is maintained for reasons of record, because the sapCDEF genes have not been clearly defined by the nucleotide sequence or nucleic acid molecule, that encodes the corresponding proteins that are expressed, as now claimed.

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17. Applicant argues the rejection of claims 1-2, 6-8 under 35 U.S.C. 102(a) as being anticipated by Dworkin et al (March 1996) by asserting:

a. Dworkin did not teach or suggest making and using mutant strains that express foreign heterologous protein for vaccination purposes as claimed in the present invention.

18. Applicant's arguments filed with respect to Dworkin et al have been fully considered but they are not persuasive because:

i. The intended use of the claimed compositions does not define over the prior art applied to the claims

19. The rejection of claims 14,16 under 35 U.S.C. 102(b) as being anticipated by Dworkin et al (June 1995) is argued to:

a. be drawn to the cloning of sapB gene which is totally different from sapCDEF gene.

b. The function of sapB is to serve as a surface protein that is involved in antigenic variation, while sapCDEF serves as a transporter involved in translocation of protein across the bacterial envelope.

c. The reference did not teach sapCDEF gene.

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20. Applicant's arguments filed Dworkin et al (June, 1995) have been fully considered but they are not persuasive because:

a. The modified bacteria was a modified *Campylobacter fetus* strain that evidenced a mutation in a single gene in the *sap* locus of genes but expressed all other genes in the locus. Evidence of gene expression that would permit binding of SapA, expressed by a transformed *E. coli* strain, to the surface of the Sap- strain indicates that all of the genes that *C. fetus* would normally express were active except the *sapA* gene sequence. Inherently the modified strain of *C. fetus* would encode the *sapCDEF* genes. No specific strains of bacteria are recited in claim 14 and 16 and thus would encompass modified strains of *C. fetus* that naturally express all of the genes that are inherently present in the bacteria.

b. If the claimed strain is intended to read on a transformed bacteria, how the bacteria is modified (ie. Transformation with a specific plasmid or vector), could obviate this rejection.

21. The rejection of claims 1-2,4, 6-8 under 35 U.S.C. 102(b) as being anticipated by Blaser (November 1994 or November 1993) is argued:

a. Blaser et al did not teach or suggest using the mutant strains for vaccination purposes.

22. Applicant's arguments filed with respect to Blaser (1993 or 1994) have been fully considered but they are not persuasive because the recited intended use does not define over the prior art.

i. The composition of Blaser comprised an antigenic, therapeutic agent, that encodes for kanamycin resistance. The claimed invention is a *C. fetus* strain that comprises a

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DNA expression cassette encoding any heterologous protein antigen or therapeutic agent (claim 8), not a method of vaccination. Stedmen's medical dictionary defines kanamycin sulfate as an amino glycoside antibiotic substance derived from strains of *Streptomyces kanamycetius*; a thermostable, water-soluble, polybasic substance consisting of two amino sugars glycosidally linked to deoxystreptamine. The strains of Blaser encoded a heterologous protein for the production of kanamycin resistance. Therefore, Blaser disclosed the production of a mutant strain of *C.fetus* that comprises an antigen, that can be considered to be a therapeutic agent, wherein the DNA cassette encoded a heterologous protein antigen expressed in the mutant *C.fetus* strain.

c. The rejection made of record is maintained.

23. The rejection of claims 1-2,4-9 under 35 U.S.C. 103(a) as being unpatentable over Blaser (1994 cited above.) in view Lubitz et al (US pat. 5,470,573) is argued:

a. Blaser does not teach or suggest using the mutant strains for vaccination purposes;

b. Lubitz et al is argued;

i. to teach away because the reference does not involve modification of sap homologs in *C.fetus* ;

ii. the strains of Lubitz comprise a lytic gene; and

iii. the strains were not *C.fetus* modified strains expressing altered sap homologs for vaccinating animals.

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24. Applicant's arguments filed with respect to Blaser in view of Lubitz have been fully considered but they are not persuasive because:

i. the recited intended use does not define over the prior art.

ii. The composition of **Blaser** comprised

(1) an antigenic, therapeutic agent, specifically kanamycin, a heterologous antigen.

(2)The compositions were administered to a host animal for challenge experiments, thus stimulating an immune response. The reference used the strain to evaluate the in vivo characteristics of sapA mutant C.fetus cells through administering the strain to a mammal. Virulence was evaluated through determining the number of cells required to cause bacteremia relative to wild type strains. The reference clearly is evaluating antigenic characteristics of the strains, virulence characteristics and the immune response stimulated in the host through challenge experiments using the mutant strains. The claimed method is not a method of vaccinating, but a method of stimulating an immune response.

(3)Blaser evaluated the antigens produced by the strains through immunoblots. Clearly antigen expression and immune reactions were evaluated for the mutant Campylobacter strain carrying a heterologous antigen.

iii. Lubitz teach the construction of mutant strains from gram negative bacteria to include a strain of Campylobacter (see col. 2, line 34) that comprise S-layer proteins, the purpose of producing mutant strains of bacteria that comprises a DNA cassette encoding a heterologous

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protein antigen, wherein the heterologous antigen comprises a nucleic acid sequence for antigenic structures for human viruses, HIV (human immunodeficiency virus, HBV (hepatitis B virus and EBV (Epstein Barr virus) and other human proteins and antigens (col. 3, lines 16-24; (col. 2, lines 20-40).

iv. Lubitz was cited for what the reference taught with respect to S-layers being carrier proteins for heterologous antigens. It was known in the art, that S-layers provide a means of expressing and presenting heterologous antigens through incorporation of heterologous antigens into S-layer encoding DNA cassettes.

v. Clearly Lubitz does not teach away from the construction of a mutant *Campylobacter* strain that comprises an S-layer and comprises an expressed heterologous antigen that is encoded by a DNA cassette. Blaser clearly teaches the use of *C.fetus* as a strain that is useful for the evaluation of the immune system of a mammalian host and in evaluating the immune response to antigens expressed (immunoblot). Therefore, Lubitz and Blaser are analogous art.

vi. Both Blaser and Lubitz teach and suggest the evaluation of expressed heterologous antigens, as well as the construction of mutant strains of bacteria that comprise DNA cassettes that comprise a heterologous antigen, wherein the mutant strain is a *Campylobacter* strain. Both *C.fetus* and *C.jejuni* are both taught to be useful *Campylobacter* strains for the expression of a DNA cassette that encodes a heterologous antigen.

vii. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based

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on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

viii. In response to applicant's argument that the prior art does not teach a composition "for vaccinating an animal", a recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. In a claim drawn to a process of making, the intended use must result in a manipulative difference as compared to the prior art. See *In re Casey*, 152 USPQ 235 (CCPA 1967) and *In re Otto*, 136 USPQ 458, 459 (CCPA 1963).

Absent a showing of unexpected results, the applied prior art obviates the now claimed invention for reasons of record.

25. The rejection of claims 1-8 under 35 U.S.C. 103(a) as being unpatentable over Blaser (1994 cited above.) in view of Szostak et al (1996) are argued:

a. Blaser does not teach or suggest using the mutant strains for vaccination purposes;

b. Szostak et al is argued;

i. to teach away because the reference does not involve modification of sap homologs in *C. fetus* ;

ii. the strains of Szostak et al comprise a lytic gene; and

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iii. the strains were not C.fetus modified strains expressing altered sap homologs for vaccinating animals.

iv. Szostak et al is argued to not teach or suggest anything about S-layer proteins

v. Szostak et al is asserted to not show the use of S-layer proteins as a vehicle of foreign antigen presentation

vi. Applicant asserts there is no motivation to combine the references.

26. Applicant's arguments filed with respect to Blaser in view of Szostak have been fully considered but they are not persuasive because:

a. Blaser does administer the recombinant C.fetus strain to a host for the evaluation of challenge experiments

b. Blaser evaluated the immune response and the antigens expressed by the strain

c. The C.fetus strain of Blaser comprised a heterologous antigen for expression

d. Szostak et al (at page 193, col. 2, paragraph 2) taught that recombinant S-layers accepted foreign sequences up to 600 amino acids and serve as carriers of foreign epitopes. Incorporation of foreign antigens from both bacterial and viral origins is clearly suggested and taught for stimulation of an immune response (see last full sentence of col. 2, second paragraph). See figure 2, page 194. The construction of recombinant gram negative bacteria that express a heterologous antigen using a DNA cassette that incorporates the heterologous antigen into the recombinant S-layer is taught to provide a means for carrying relevant antigens that are not limited in size (see abstract last line and lines 9-10 of the abstract).

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e. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

f. In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, there is a reasonable expectation of success of using other relevant heterologous antigens for expression as marker proteins, as well as for stimulating an immune response because Szostak teaches that through site directed mutagenesis and structural and functional analysis S-layer domains were found to have flexible surface loops that will accept foreign sequences up to 600 amino acids, to include heterologous antigens from bacteria and viral sources and that recombinant S-layers serve as carriers of epitopes and proteins for relevant antigens (abstract). The reference teaches and suggests the formulation of HIV-I RT (viral antigen) in a mutant bacterial strain (see page 195, col. 1, paragraph 2).

g. In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., a method of

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vaccination using the claimed compositions) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

h. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

New Claim Limitations/New Grounds of Rejections

Claim Rejections - 35 U.S.C. § 112

27. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

28. Claim 1 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. While the examiner requested Applicant to claim a product that was not a product of nature, at no time did the examiner request the insertion of claim limitations not supported by the instant specification. Amendment of claim 1 to recite the negative limitation -- non-naturally occurring-- does not evidence original descriptive support and is therefore NEW

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Matter. Applicant may claim any embodiment that is described in the instant specification but the recitation of the phrase "non-naturally occurring" could not be found by the examiner in the specification. Amendment of the claim with an equivalent phrase that evidences original descriptive support is requested. It was noted that claim 3 has been canceled that previous claimed that the heterologous protein was a S-layer protein which would read on natural recombination that occurs in *C.fetus*.

29. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

30. Claim 18 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claim 18 recites a clarification phrase "wherein all but one of **the sapA homologs** are altered due to the insertion of said DNA cassette." Claim 1 does not provide antecedent basis for the phrase "the sapA homologs" and therefore is vague and indefinite. In view of the prior art teaching the existence of multiple homologs and the number of homologs can possibly vary from one strain to another, how many of the sapA homologs are mutated in what strains is not distinctly claimed. How many and what genes have insertions is not clear for the limitations recited in the claim. Incorporation of the claim limitations into claim 1 that are being clarified could possibly obviate this rejection.

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Allowable Subject Matter

31. Claim 15 is objected to as being dependent upon a rejected base claim, if rewritten in independent form including all of the limitations of the base claim and any intervening claims, as well as a deposit of the genetic material contained therein to meet the requirements of the Budapest Treaty, would define allowable subject matter.

Conclusion

No claims are allowed.

This is a non-Final rejection.

32.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ginny Portner whose telephone number is (703)308-7543. The examiner can normally be reached on Monday through Friday from 7:30 AM to 5:00 PM except for the first Friday of each two week period.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached on (703) 308-3909. The fax phone number for this group is (703) 308-4242.

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The Group and/or Art Unit location of your application in the PTO will be Group Art Unit 1645. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to this Art Unit.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Vgp

October 18, 2000

L. F. Smith
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